Task-force in Europe for Drug Development for the Young

Funded under
VI Framework Programme

Project Number: LSHB-CT-2005-005216

TEDDY

TASK-FORCE IN EUROPE FOR DRUG DEVELOPMENT FOR THE YOUNG

INSTRUMENT: NETWORK OF EXCELLENCE

THEMATIC PRIORITY: LIFE SCIENCES, GENOMICS AND BIOTECHNOLOGY FOR HEALTH

Publishable Executive Summary

TD-REP.016-Annex1_Publishable_Executive_Summary.doc

PERIOD COVERED: FROM 01 JUNE 2008 **TO** 31 MAY 2009

START DATE OF PROJECT:	01 JUNE 2005
DURATION:	5 YEARS
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PROJECT COORDINATOR ORGANISATION NAME:	CONSORZIO PER VALUTAZIONI BIOLOGICHE E FARMACOLOGICHE (CVBF)

REVISION DATE:	DRAFT	FINAL
		12 JANUARY 2010

Document Profile					
Code		**Title**		**Visibility**	
TD-REP.016-Annex1		Publishable Executive Summary		PUBLIC	
Drafted by	**Date**	**Submitted by**	**Date**	**Approved by**	**Date**
P.Mincarone	12/01/10	A. Ceci	12/01/10	Objectives Coordinators	N.A.
Approved by	**Date**	**Approved by**	**Date**	**Approved by**	**Date**
Executive Board	N.A.	Ethics Advisory Group	N.A.	Network Governing Council	N.A.
Aim of the document				**Receivers**	
This Publishable interim activity report, is aimed at briefly illustrating what has been done in the IV year.				European Commission Anyone interested in the project	
Pertinent WP		**Reference activity**			
10		A079-Prepare Annual reports			

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1. Authors

Table 1: list of authors

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2. Aim of the document

This Publishable Executive Summary, part of the Annual Activity Report, is aimed at illustrating in a summary way what have been done in the IV year project.

3. Content: Publishable Executive Summary

3.1. Summary description of project objectives

The **Task-force in Europe for Drug Development for the Young - TEDDY** is a Network of Excellence funded under the Sixth EU Framework Programme for Research and Technological Development (FP6).

The project started in June 2005 and is expected to run until 2010. It involves 19 partners from 10 EU countries and Israel (one of the partners, I.RI.D.I.A. SrL have joined the network from 1 June 2006).

The overall aim of TEDDY is promoting the availability of safe and effective medicines for children in Europe (optimisation for the paediatric use of current drugs and promotion of the development of new drugs) by integrating existing expertise and good practices, as well as stimulating further developments also by let children benefit from breakthroughs in genomics, biotechnology, pharmacology and therapeutics.

The proposed network will involve different stakeholders active in both drug development sector and paediatric clinical practice. European academics, researchers, healthcare specialists and ethics experts will work together with pharmaceutical companies, regulatory agencies and patients associations to attain common objectives.

TEDDY NoE is organized in 12 Work Packages (WPs) as reported in the following table.

ID	WP Name
1	Pharmacoepidemiology
2	Facilitation of the advancement of genomics and paediatric pharmacogenetics studies
3	Methodology of clinical studies in paediatrics
4	Addressing key therapeutic questions in children
5	Rare diseases
6	Post-marketing studies applied to paediatric medicines
7	Ethics
8	Paediatric drug database
9	Communication, Information & Learning
10	Management of the network
11	Collaboration with other initiatives and organizations
12	Gender issues on drug evaluation

3.2. Contractors involved

Contractor	Country	Internet WEB site
Consorzio per valutazioni Biologiche e Farmacologiche	Italy	www.cvbf.net
Azienda Ospedaliera di Padova	Italy	www.sanita.padova.it
UNIVERSITY COLLEGE LONDON	United Kingdom	www.ucl.ac.uk
Rijksuniversiteit Leiden	The Netherlands	www.lacdr.nl
Consiglio Nazionale delle Ricerche – Istituto di Tecnologie Biomediche	Italy	www.itb.cnr.it
Erasmus University Medical Center	The Netherlands	www.eur.nl
Istituto Superiore di Sanità	Italy	www.iss.it
ROMANIAN ANGEL APPEAL FOUNDATION	Romania	www.raa.ro

Contractor	Country	Internet WEB site
Linköpings universitet	Sweden	http://www.liu.se
Institut National Santé et Recherche Médicale	France	www.inserm.fr
MEDICAL RESEARCH COUNCIL Clinical Trials Unit	United Kingdom	http://www.mrc.ac.uk/
HOSPITAL CARLOS III	Spain	www.hcarlosiii.com
UNIVERSITE DE LIEGE	Belgium	www.ulg.ac.be
Institute of Physiology, Academy of Sciences	Czech R.	http://www.biomed.cas.cz/
Technion - Israel Institute of Technology - The Bruce Rappaport Faculty of Medicine	Israel	www.technion.ac.il
Charité Universitätsmedizin Berlin	Germany	http://www.charite.de/start/
Tecnofarmaci – Società Consortile per Azioni – per lo Sviluppo della Ricerca Farmaceutica	Italy	www.tecnofarmaci.it
School of Pharmacy	United Kingdom	http://www.ulsop.ac.uk/depts/paediatric-pharmacy-research/cppr.htm
I.RI.D.I.A. S.r.L.	Italy	www.iridia.eu

3.3. Co-ordinator contact details

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3.4. Reference to the project public website and logo

Figure 1: TEDDY Logo

Public WEB site URL: http://www.teddyoung.org/

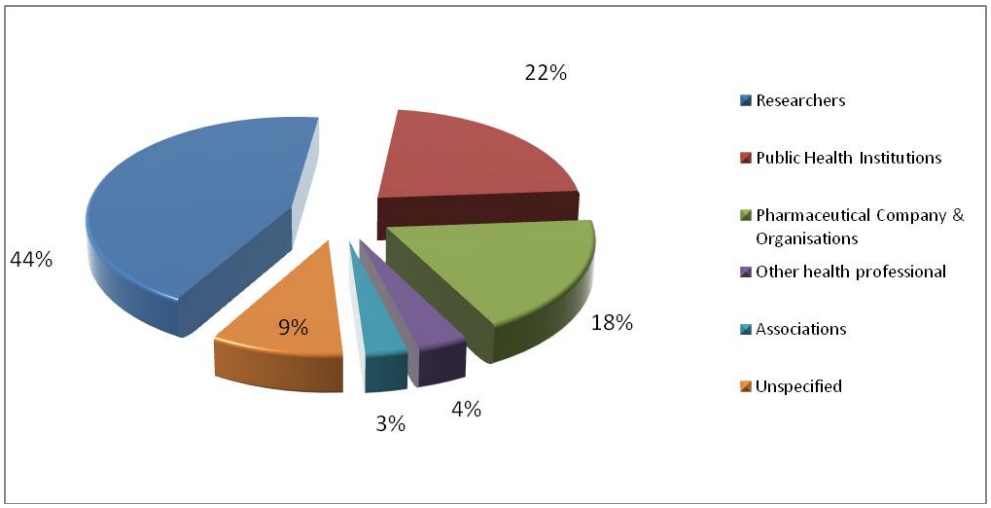
3.5. Work performed

The first mission of TEDDY, being a network of Excellence, is to create the condition to foster the relationships among stakeholders involved in the development of drugs for children.

TEDDY dedicated the first 3 years mainly to the building of the network (both internal and external relationships). The forth year has been focused to disseminate the results and to strengthen the external collaborations (training initiatives, research proposals drafting and submitting, participation to external initiatives to increase the dissemination). The impact of these actions can be measured by means of some indicators:

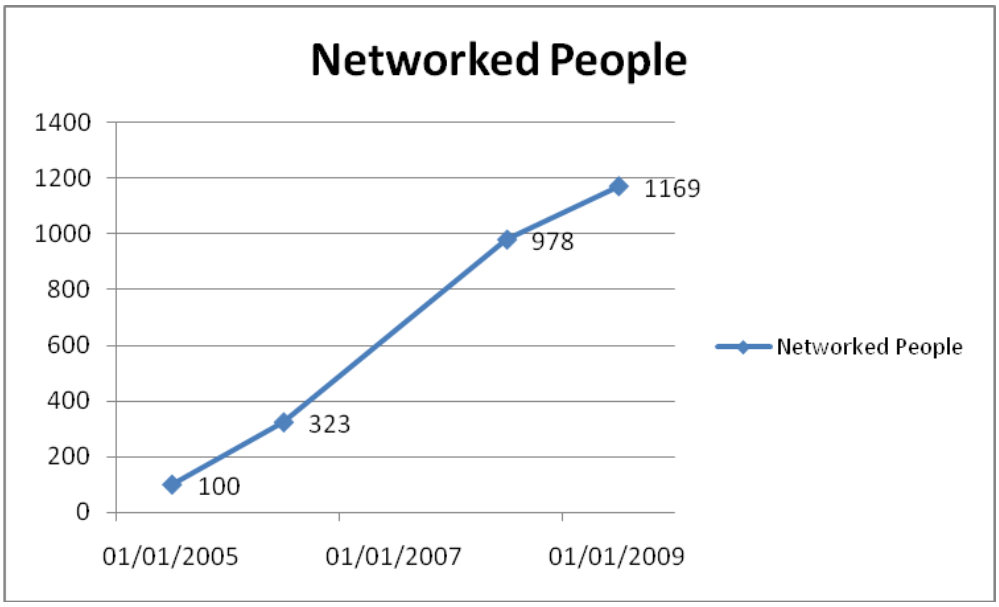
- the contact list, created to support interaction with stakeholders (invitation to TEDDY meetings, invitations to surveys, joint participation in calls for proposals, newsletters sending, etc.) has 1.168 registered contacts. The contact list is an essential tool that allow to plan, execute and verify each action that requires collaboration. 101 out of 1.052 asked to be registered through the WEB site. Figure 1 illustrates the distribution among the different stakeholders categories.

Figure 2: Contacts distribution by categories



In the following figure the evolution of the network in terms of number of people is shown with respect to three important phases: at the start of the project, after one year of activities and at the end of the forth year.

Figure 3: network growth



- 1.052 people are presently registered for regularly receiving the TEDDY Newsletters (NLs) (only 12 out of the 1.064 contacted, asked to be removed form the list, showing that more than 98% are likely to be interested in the NLs content);
- Until May 2009, 38 times TEDDY members have been invited as speakers in external meetings to report on some of the results of TEDDY NoE (2 during the first year, 4 during the second, 21 during the third and 11 during the forth);
- On the contrary, 69 times external experts accepted to participate as speakers in TEDDY NoE meetings;
- 6 projects proposals have been submitted under FP7 and under the European Public Health Program by several large consortia involving two or more TEDDY NoE partners. To date, 2 out of 6 have been selected for funding.
- Attendees evaluations for the Open conferences held in the 4th year (Marseille, June 2008 and Madrid, January 2009); among others, the following questions were answered by participants:
    - *How do you evaluate the SIGNIFICANCE of the topics with respect to your needs*? High/Very High: 76%;
    - *How do you evaluate the QUALITY of the information*? High/Very High: 79%;
    - *How do you think the event has contributed to the increment/improving of your RELATIONSHIPS with other subjects*? Good: 76%;
    - *How did you rate the PLANNING/ORGANIZATION of the event*? Good: 87%;

  More details are reported in the two documents that summarizes the meetings (*TD-D113-Third_meeting_TEDDY_objectives.pdf* and *TD-REP.016-Annex4_Marseille_Meeting.pdf*).

Three surveys are currently on going to collect opinions, expectations, suggestions from several kind of stakeholders:

- Socio-economic impact of the European paediatric regulation on **pharmaceutical industries** (TEDDY can count on 347 pharmaceutical contacts – gathered by its own partners and by the data published by the EMEA on its WEB site – for this survey).
- Relevance of multicentre collaborative **research** in pharmacogenetic studies in paediatrics.
- Involvement of **Ethics Committees** (ECs) in paediatric research in Europe (the aim of the survey is to evaluate the impact of the new paediatric European ethical and regulatory framework on Ethics Committees in charge of reviewing paediatric research protocols). An inventory of ECs operating in Europe was carried out by TEDDY NoE collecting contact information on more than 830 ECs.

Besides the Pharmaceutical Industries and the Ethical Committees, the other main category of stakeholder to which the efforts of TEDDY is addressed is represented by **key experts** that have been included in an *Independent Consultation Forum*. These key people have been requested to express an evaluation on the results produced by TEDDY and on the possibilities to further use them. They have received the main products of the network among which it is useful to mention a monograph published in 2009 that summarizes the

activities of the network: A. Ceci, et al. *The EU Paediatric Regulation*. Pharmaceuticals Policy and Law, Vol. 11 (1,2), 2009, 1-110. Indexed in EBSCO database (some of the included articles are *TEDDY NoE project in the framework of the EU Paediatric Regulation, presenting the TEDDY project and the results obtained in the first 3 years of activities*; *A European Paediatric Medicines Database (EPMD), presenting TEDDY EPMD and the analysis carried out to discuss the 'state of the art' of paediatric medicines licensed by European Medicines Agency (EMEA) in its first 12 years of activities*; *Off-label and unlicensed use of medicines for children*; *Recommendation for Drug Development for Children*; *Clinical trials for paediatric medicines in Europe*; *Activity of Ethics Committees in Europe on issues related to clinical trials in paediatrics*; *Availability of medicines for rare diseases in EU Countries*).

Moreover, TEDDY experts groups have continued their activities of support and contribution to the EMEA and to the European Commission by releasing comments and suggestions to the following documents:

- EMEA/CHMP Working Group with Healthcare Professionals' Organisations (HCP WG) - Final Recommendations and Proposals for Action;
- Committee for Medicinal Products for Human Use (CHMP) - Guideline on the clinical development of medicinal products for the treatment of Cystic Fibrosis;
- Updated priority list – revised for studies into off-patent paediatric medicinal products;
- Suggestions for the research themes under the Framework Program 7 (see WP12).

The main results achieved within the 12 WorkPackages during the IV year are reported hereunder.

WP1 finalised the work from the previous 3 years in terms that a total of 4 manuscripts were finally published in peer-reviewed journals one of which was BMJ. Also the potential to minimise paediatric medication errors was explored and a review has been published on this topic. WP1 also further investigated the use of drugs in specific therapeutic areas. WP1 represented TEDDY at the 11th Biannual Conference of the European Society of Developmental and Paediatric Pharmacology.

WP2: During this year a second position paper entitled "Integration of pharmacogenetics and pharmacogenomics in paediatric drug development: implications for regulatory submission and medical decision making" has been written in the form of a guidance document and submitted to the Journal of American College of Clinical Pharmacology. The paper highlights the lack of translational research protocols in pharmacogenetics and the low uptake of genetic information into drug labelling. In addition, a quantitative assessment was performed to compare the degree of concordance between the contents of EPARs following market authorisation application and existing requirements for approval and label claims in paediatric indications, as defined in current guidelines for special populations and ICH E11. This paper was scheduled for submission in July 2009. Furthermore, a collaborative project between the University of Leiden and the University of Linköping was initiated in February 2009 to evaluate the correlation between treatment response and pharmacogenetic factors in neuroblastoma. The main objective of this investigation is to identify whether polymorphisms in the pharmacokinetics of drugs currently prescribed to paediatric patients are associated with poor prognosis. These efforts will also be summarised in a manuscript to be submitted for publication in August 2009.

WP3 experts group identified the topics to be handled in the "Recommendation for clinical trials in children", a position paper aiming at revising and critically assessing methodological key issues in performing clinical trials in paediatrics. Proposed authors were contacted and first draft contributions were collected. Moreover, a paper evaluating the status of paediatric clinical trials performed for drugs to be used in children to verify their methodology and their compliance with the Note for Guidance ICH Topic E11 ("Clinical trials for paediatric medicines in Europe") was included in the TEDDY Monograph, The EU Paediatric Regulation. TEDDY Network of Excellence, published in Pharmaceuticals Policy and Law.

WP4: therapeutic Experts Groups (TEGs) continued their activities of support and contribution to the EMEA and the European Commission by releasing comments and suggestions to their documents and guidelines. A paper identifying the unmet therapeutic needs for the development and use of medicinal products in male/female children ("Recommendation for Drug Development for Children") was published in Pharmaceuticals Policy and Law as part of TEDDY Monograph, The EU Paediatric Regulation. An active contribution to the EMEA-PDCO in drafting the 2009 Priority List has been done with success.

The **WP5** is carrying out a literature review on the epidemiology of selected RD in Europe, identified on the basis of their system/organ involvement, paediatric onset of age, complexity of the disease and availability of treatment. The WP5 established additional contacts with rare diseases and orphan drugs experts in order to collect further information and opinions on challenges to guarantee availability of orphan drugs across EU.

WP6 mainly studied ADR reporting in children using data from both the WHO database on spontaneous ADR reporting as well as data from the IPCI and Pedianet database. Within the WHO database, first the reporting odds ratios for some adverse drug reactions of interest were calculated. These ADRS were liver toxicity, all ADRs related to the use of prokinetic drugs and to the use of gastric acid suppressing drugs and all ADRs related to the use of anti-asthmatic drugs. Based on the findings of these analyses, nested case-control studies have been initiated studying the relationship between the use of gastric acid suppressing drugs – the use of anti-asthmatic drugs and the outcomes of interest.

A Survey has been prepared to evaluate the socio-economic impact on pharmaceutical industries of the REGULATION (EC) NO 1901/2006 ON MEDICINAL PRODUCTS FOR PAEDIATRIC USE after its first 2 years of application. Results will be delivered, in an anonymous form, to the EMEA and to the European Commission.

WP7: the main achievement of WP7 was the organization, with the Espace Ethique Méditerranéen (the Bioethics research centre of the Université de la Méditerranée – Marseille), of the TEDDY European Symposium on Ethics and paediatric clinical research in Europe (Marseille 19-20 June 2008). This event was addressed to representatives of national, European and International Institutions (e.g. EMEA, Clinical Trials Facilitation Group of Medicines Agencies, ONU – Commission for the rights of the Child) as well as to representatives of commercial and non-commercial sponsors, researchers, patients' associations and ethics committees. One of the main outputs of the Symposium was the identification of criteria to set up *Recommendations on Ethical issues on Medicine for children for Industry*. Many other initiatives (courses, lectures and international mission) were held to stimulate debate on ethical issues arising from paediatric clinical research and to disseminate information by means of training and education activities. Moreover, the "Survey on the involvement of Ethics Committees (ECs) in paediatric research in Europe" was planned and started in order to evaluate the impact of the new paediatric European ethical and regulatory framework on Ethics Committees in charge of reviewing paediatric research protocols.

WP8: During the year the European Paediatric Medicines Database has been further implemented by the inclusion of data on 97 paediatric medicines, 187 paediatric clinical trial descriptions, prices in 7 European countries. The FAQ area on TEDDY website was implemented at the end of 2008. Two manuscripts were drafted and included in TEDDY Monograph published on Pharmaceuticals Policy and Law. D091 - Statistical analysis of FAQs and D123 - Third Report on paediatric drugs available for children were removed.

WP9: The e-learning platform is available on the TEDDY WEB site or directly accessible from http://www.teddylearning.org/Default.aspx. A new e-learning plan was drafted to highlight the most significant results produced by TEDDY. The first two courses "Children are not little adults" and "the European Paediatric Regulation" are completed and available, while the other ones will be delivered by the end of the project (the detailed plan of delivery is reported in the task A064). D097 - Online package was merged with D126-Informative packages on TEDDY aims and activities for Patients and Parents associations. The new deliverable's (D126 - Informative packages on clinical trials for Patients and Parents) deadline was postponed to March 2010; collaboration will be sought with the FP7 project RESPECT (Relating Expectations and Needs to the Participation and Empowerment of Children in Clinical Trials).

WP10 TEDDY organized the open meeting "INNOVATING PAEDIATRIC RESEARCH IN EUROPE" that has been held in Madrid (29-30 January 2009) to promote a deep and wide analysis of the Paediatric Research situation in Europe, from different points of view: authorities, industry, scientific societies, health institutions and researchers, all of them inside the framework of TEDDY NoE.

Moreover, TEDDY took part in several meetings organized by external entities and, among the others, it was invited to participate at the 1st EMEA Workshop on European Paediatric Networks (London, 16 February 2009) and at the workshop organised by the US National Institute of Child Health and Human Development to collect a set of expectations and specifications for the establishment of a national paediatric drug and device development platform for the Clinical and Translational Science Awards (CTSA), a National Institutes of Health (NIH) program to build clinical and translational infrastructure.

TEDDY is fully involved in the submission of projects under the FP7 dealing with research on paediatric drugs.

WP11: Work has been dedicated to prepare dissemination material on TEDDY aims and activities. In particular 250 copies of the monograph, A. Ceci, et al. The EU Paediatric Regulation. Pharmaceuticals Policy and Law, Vol. 11 (1,2), 2009, 1-110, were bought in order to be distributed during TEDDY main dissemination events.

Moreover, in the frame of studying the socio-economic impact of the EC Regulation 1901/2006 on medicinal products for paediatric use on the pharmaceutical industries (D075), an ad hoc questionnaire was drafted, in close cooperation with WP6, and used to design the on-going survey on the socio-economic impact. Besides the analysis of the concrete changes produced from this perspective, the questionnaire aims at investigating any concrete support needed by the companies interviewed to comply with the Regulation, in an attempt to create a closer contact between TEDDY and Industry representatives.

WP12 mainly worked in the preparation of two documents: the final version of a databank of information on basic research and gender based biology and a suggestion addressed to the European Commission of R&D topics on gender issues to be included in future calls of the FP7.

3.6. Main elements of the plan for using and disseminating the knowledge

TEDDY continuously produces knowledge and spreads it through different ways and experiences:

- TEDDY meetings: TEDDY has planned meetings that are open to external stakeholders.
- Publications: one of the most important thing TEDDY has to do is to make explicit its activities to foster the collaboration with external partners involved in the area of the Health for children. To this aim, TEDDY partners are involved in the preparation of scientific articles in terms of reviews and position papers. The following articles were published / submitted to date:
    - **MONOGRAPH**
        - A. Ceci, et al. *The EU Paediatric Regulation*. Pharmaceuticals Policy and Law, Vol. 11 (1,2), **2009**, 1-110. Indexed in EBSCO database.

          This monograph, part of the activities TEDDY carried out to achieve its aim, is constituted by the following 11 articles:

            - F. Donnelly. *New paediatric research initiatives in the European Union, proving an overview of the EU research initiatives in the field of paediatrics*;
            - A. Ceci, P. Baiardi, F. Bonifazi, C. Giaquinto, M.J. Mellado Peña, P. Mincarone, A. Nicolosi, M. Sturkenboom, I. Wong. *TEDDY NoE project in the framework of the EU Paediatric Regulation*, presenting the TEDDY project and the results obtained in the first 3 years of activities;
            - E. Krekels, A. Ceci, A. Iolascon, S. Girotto, O. Della Pasqua. *The role of paediatric pharmacogenetic studies in Europe*, exploring the current status, limitations and perspectives of pharmacogenomic and pharmacogenetic clinical research in the paediatric population;
            - M. Felisi, R. Padula, F. Bartoloni, I. Grosch-Wörner, B. Kagedal, M.J. Mellado Peña, J. Parry, A. Stuchlik, K. Verhamme, A. Ceci. *TEDDY EPMD: a European Paediatric Medicines Database (EPMD)*, presenting TEDDY EPMD and the analysis carried out to discuss the 'state of the art' of paediatric medicines licensed by European Medicines Agency (EMEA) in its first 12 years of activities;
            - A. Neubert,M. Felisi, A. Bonifazi, C. Manfredi, I.C.K. Wong, A. Ceci. *Off-label and unlicensed use of medicines for children*, referring on the results of a survey carried out to reach a common definition of the terms off-label and unlicensed use of medicines in children to favour the use of a European official regulatory terminology and facilitate pharmaco-epidemiological research;

- M. Sturkenboom, M. Felisi, C. Manfredi, A. Neubert, L. Cantarutti, R. Padula, F. Sen, K. Verhamme. *Paediatric status and off-label use of drugs in children in Italy, United Kingdom and the Netherlands*, comparing the extent of the off-label use in Italy, United Kingdom and The Netherlands;
- M. Catapano, C. Manfredi, P. Paolucci, H. Cross, K. Verhamme, M.J. Mellado Peña, I. Grosch-Wörner, C. Knibbe, A. Ceci. *Recommendation for Drug Development for Children*, identifying the unmet therapeutic needs for the development and use of medicinal products in male/female children;
- P. Baiardi, S. Girotto, O. Della Pasqua, L. Harper, I. Grosch-Wörner, A. Ceci, C. Giaquinto. *Clinical trials for paediatric medicines in Europe*, evaluating the status of paediatric clinical trials performed for drugs to be used in children to verify their methodology and their compliance with the Note for Guidance ICH Topic E11;
- A. Altavilla, C. Giaquinto, D. Giocanti, C. Manfredi, J.-P. Aboulker, F. Bartoloni, E. Cattani, M. Lo Giudice, M.J. Mellado Peña, R. Nagler, C. Peterson, O. Vajnerova, F. Bonifazi, A. Ceci. *Activity of Ethics Committees in Europe on issues related to clinical trials in paediatrics: results of a survey*, referring on the results of a survey carried out to examine the measures enforced by Member States to implement the EU Clinical Trials Directive and other ethical norms relevant for clinical research in paediatrics;
- K. Verhamme, F. Bonifazi, A. Ceci, P. Elferink-Stinkens, M. Murray, A. Neubert, A. Nicolosi, B. Stricker, I. Wong, M. Sturkenboom. *Adverse Drug Reactions (ADRs) reporting in children*, studying the frequency and the type of ADR reporting in children;
- A. Trama, D. Pierannunzio, A. Loizzo, D. Taruscio, A. Ceci. *Availability of medicines for rare diseases in EU Countries*, referring on the results of a questionnaire, aimed at collecting information on orphan medicinal products availability, administered to twelve Member States.

- **PEER REVIEWED PUBLICATIONS**
  - Adriana Ceci, Carlo Giaquinto, Jean-Pierre Aboulker, Paola Baiardi, Fedele Bonifazi, Oscar Della Pasqua, Alfredo Nicolosi, Domenica Taruscio, Miriam Sturkenboom, and Ian Wong. *The Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence*. Pediatr Drugs **2009**; 11 (1): 18-21[1].

[1] Full article available at: http://pediatrics.adisonline.com/pt/re/pdd/abstract.00148581-200911010-00008.htm;jsessionid=JryFfpnkV5HRDFnwNPpz3Lnq7q3t2nVxYPqQvpkQDc0hMzn6rWGy!-1010963402!1811956291&8091!-1

TEDDY NoE supports existing paediatric networks, societies and regulatory bodies to stimulate innovation, especially when such initiatives depend on external support. In its first three years, the network has so far concentrated on highlighting the implications and requirements of the *European Regulation*, establishing consensus around terms and instruments used in research, and fostering closer relationships across EU countries. This work has resulted in a number of papers and abstracts featured in peer-reviewed journals, with further reports also available on the project website at www.teddyoung.org.

For the researchers and scientists involved, a key issue remains the need for consensus on best practice in development and use of medicines for children. This presents the ongoing problem of stakeholders across Europe agreeing on paediatric research requirements, and TEDDY will continue to approach this challenge and adapt to meet it.

- Annagrazia Altavilla. *Clinical research with children: the European legal framework and its implementation in French and Italian law*. European Journal of Health Law, vol.15, 2008, pp.1-17[2]

  The International Convention of the Rights of the Child states that children's rights in Europe should be better protected by applying the principle of best interests, and by developing the legal frameworks encompassing paediatric clinical research.

  The ethics team within the *TEDDY NoE* has provided an overview of how the European legal framework governs clinical research on minors, published in The European Journal of Health Law. Using a comparative approach, the author explores the lack of harmonisation between different international and European ethical/legal statements. The impact this has on national legislation is evaluated by analysing provisions that have been planned Italy and France as part of their national ratification/implementation of the EU directive on medicinal clinical research.

- Paolo Paolucci, Kathy Pritchard Jones, Maria del Carmen Cano Garcinuno, Mariana Catapano, Achille Iolascon, Adriana Ceci. *Challenges in prescribing drugs for children with cancer*. Lancet Oncol. 2008 Feb;9 (2):176-83 18237852 (P,S,E,B)[3]

  Despite the limited availability of drugs specifically studied for use in children with cancer, paediatric oncology has nonetheless achieved high cure rates. While the efficacy of the drugs used has often been the main concern, the authors call for more attention to be directed to the permanent side-effects for growing children.

[2] Full article available at: http://www.ingentaconnect.com/content/mnp/ejhl/2008/00000015/00000002/art00002?token=0045146df1557e442f20675d587634702c496e6c2a7a6a687630505db76fd7162c794

[3] Full article available at: http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(08)70030-5/abstract

Incorrect dosing in specific age groups can result from the lack of pharmacokinetic data, dose-defining studies, schedules defined by age and appropriate formulations. This in turn can potentially cause resistance development, increased adverse drug reactions and a lack of benefit for the patient.

Since 2003, these major clinical concerns have driven European initiatives for a Paediatric Regulation to improve the risk-benefit ratio of such drugs for children and to also provide a legal framework to address past limitations. This progress does not however also provide the funding needed to conduct appropriate studies of these drugs within this setting, but Europe is now addressing the present difficulties of drug prescribing for children with cancer by introducing measures that will encourage new public-private partnerships.

Increased cooperation between researchers and drug developers is a key aim of the new regulation, so stakeholders such as researchers, paediatric oncologists, learned societies, regulatory agencies, national agencies and pharmaceutical companies must all familiarise themselves with the opportunities created if the intended benefits for European children are to materialise.

- Antje Neubert, Miriam CJM Sturkenboom, Macey L. Murray, Katia MC Verhamme, Alfredo Nicolosi, Carlo Giaquinto, Adriana Ceci and Ian CK Wong On behalf of the TEDDY Network of Excellence. *Databases for pediatric medicine research in Europe—assessment and critical appraisal*. Pharmacoepidemiol Drug Saf. 2008 Dec;17(12):1155-67.[4].

  The purpose of this paper is to identify and describe European healthcare databases suitable for paediatric pharmacoepidemiological research. This involved a web-based survey of all European databases to identify their nature, size, cost and accessibility as well as what demographic, clinical and drug-related information they contain.

  The survey revealed that there are numerous European healthcare databases and these contain a lot of data potentially useful to paediatric pharmacoepidemiological researchers. The TEDDY researchers initiating this work conclude that the focus of future research should be on a methodology of integrating content from the available databases, thus allowing effective use of the full potential available.

[4] Full article available at: www.ncbi.nlm.nih.gov/pubmed/18979461

- Antje Neubert, Ian C.K. Wong, Alessandro Bonifazi, Mariana Catapano, Mariagrazia Felisi, Paola Baiardi, Carlo Giaquinto, Catherijne A.J. Knibbe, Miriam C.J.M. Sturkenboom, Maisoon A. Ghaleb and Adriana Ceci. *Defining off-label and unlicensed use of medicines for children: Results of a Delphi survey*. Pharmacol Res. 2008 Nov-Dec;58(5-6):316-22.[5].

  A Delphi survey has developed common definitions of 'unlicensed' and 'off-label' drug use in children for research and regulatory purposes, a key area of concern for the European scientists who conducted it for the TEDDY network.

  Following a review of the literature available about unlicensed/off-label definitions, the researchers organised a two-stage and web-based Delphi survey targeting European experts. The questions explored opinions on problems, regulations and scenarios regarding unlicensed and off-label use of medicines. The survey findings were shown to the European Medicines Agency (EMEA) before proposed definitions derived from the survey and discussions were presented back to participants.

  The target participants were 84 scientists, health professionals, pharmaceutical companies and regulatory agencies, of which 34 fully participated through the questionnaire rounds. Consensus was attained for the majority of questions, and was lowest around questions relating to differing formulation and whether a drug was used despite being contraindicated. By the final round, 85% of the participants agreed to a proposed definition for 'off-label' ("use of a drug already covered by a Marketing Authorisation, in an unapproved way") and 80% agreed on a definition for 'unlicensed' ("use of a drug not covered by a Marketing Authorisation as medicine for human use").

  The outcomes of this consultative work contribute to pharmacoepidemiological studies and to improve comparison across different countries. The *TEDDY NoE* Delphi panel agreed that the resulting definitions should be distributed throughout the scientific community and promoted to the relevant regulatory authorities for widespread adoption.

- Annagrazia Altavilla, Carlo Giaquinto, Adriana Ceci. *European survey on ethical and legal framework of clinical trials in paediatrics: results and perspectives*. International Journal of Bioethics, vol. 18 n.3, 2008 pp 17-48[6].

[5] Full article available at: http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WP9-4TG9HV6-1&_user=2675265&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000058523&_version=1&_urlVersion=0&_userid=2675265&md5=23b2ed4712f1637e7379e0c94804409e

[6] Full article available at: http://www.cairn.info/resume.php?ID_ARTICLE=JIB_193_0015

TEDDY NoE participants from across Europe collaborate on the development of harmonised ethical perspectives relating to drug development for the young.

TEDDY NoE activities relating to ethics are designed to increase awareness among researchers and the public by engaging in a debate on ethical issues relating to paediatric drug research and usage, thus ensuring the best possible protection for children involved in clinical trials. As part of this engagement the network has conducted a survey of existing European ethical and legal frameworks for paediatric clinical trials.

The survey covered 23 EU countries and additional 4 countries associated with the Fifth and Sixth European Research Framework Programme. The aim was to highlight differences in legislation across European countries in respect of consent/assent procedures, as well as to compare the degree of paediatric specialisation within the national ethics committees charged with reviewing protocols that describe proposed studies.

A study of the findings shows that, despite a European Parliament's Directive 2001/20/EC which specifically addresses this issue, the value attributed to the will of a child who is participating in clinical trials differs across Europe. While there is a general requirement for written consent from the child's legal representative, some countries also have specific rules ensuring that the child's own opinion should increasingly carry more weight in the final decision about participation in a drug trial, with segmented age groupings provided to add weight to child's opinion based on age. The researchers also found that only four European countries have ethics committees dedicated to minors, an illustration of the lack of detailed information and debate in Europe relating to the particular ethical issues arising in paediatric clinical trials, and in addition they present an overview of the possible legal deviations implied.

- Miriam CJM Sturkenboom, Katia MC Verhamme, Alfredo Nicolosi, Macey L Murray, Antje Neubert, Daan Caudri, Gino Picelli, Elif Fatma Sen, Carlo Giaquinto, Luigi Cantarutti, Paola Baiardi, Mariagrazia Felisi, Adriana Ceci, Ian CK Wong, on behalf of the TEDDY European Network of Excellence. *Drug use in children: cohort study in three European Countries*. BMJ. 2008 Nov 24;337:a2245. doi: 10.1136/bmj.a2245[7].

[7] Full article available at: http://www.bmj.com/cgi/content/full/337/nov24_2/a2245

Increased concern over recent years about gaps in the evidence relating to the efficacy and safety of medicines used in children, a specific concern of the *TEDDY NoE* which carried out the study described here, has led to new legislation both in Europe (2007) and the United States (2003), as well as a 2007 WHO campaign to 'make medicines child size'.

The objective of this retrospective cohort study (2000-5), published by BMJ (2008;337: a2245), was an overview of drug use in children based on findings from Italy, the Netherlands and the United Kingdom. It was applied to primary care research databases (*IPCI* in the Netherlands, *IMS-DA* in the United Kingdom and *Pedianet* in Italy) covering almost 700.000 children aged up to 14 (Italy) or 18 (UK and Netherlands).

An overview like this, showing outpatient paediatric prescription patterns in a large European population, provides information useful in prioritising paediatric therapeutic research needs. As a result of their findings, the *TEDDY NoE* researchers noted that information on the safety and efficacy of some of the most commonly used drugs in children (such as oral contraceptives, steroids, and triazoles/imidazoles) is inadequate, and that not all such drugs are on the list of those needing more research.

- Rani F, Murray ML, Byrne PJ, Wong ICK. Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. Paediatrics 2008 May;121(5):1002-9[8].

[8] Full article available at: http://pediatrics.aappublications.org/cgi/content/abstract/121/5/1002

- OBJECTIVE. To study the epidemiologic features of antipsychotic prescribing to children in general practice in the UK. METHODS. A total of 384 participating general practices from the UK General Practice Research Database were used to identify 0 to 18 years patients who were prescribed ≥1 antipsychotic medication between January 1, 1992, and December 31, 2005. Annual age-specific prevalence and incidence of antipsychotic prescribing were calculated. RESULTS. The overall prevalence of use of all antipsychotics increased from 1992 (0.39 users per 1000 patient-years) to 2005 (0.77 users per 1000 patient-years). The prescribing prevalence for patients 7 to 12 years of age almost tripled between 1992 (0.23 users per 1000 patient-years) and 2005 (0.61 users per 1000 patient-years). Atypical antipsychotic prescribing increased 60-fold from 1994 (0.01 users per 1000 patient-years) to 2005 (0.61 users per 1000 patient-years). However, typical antipsychotic prescribing decreased significantly from 2000 (0.44 users per 1000 patient-years) to 2005 (0.18 users per 1000 patient-years). The incidences for typical and atypical antipsychotics showed trends similar to those of the respective prevalence. However, the overall incidence (number of new starters) for all antipsychotics was relatively stable between 1992 and 2005, which suggests that patients remain on treatment longer. CONCLUSIONS. The overall prevalence of antipsychotics almost doubled between 1992 and 2005; however, the rate of increase was much lower than the reported figures in the United States. The prescribing of atypical antipsychotic drugs has increased despite the lack of conclusive evidence showing their superiority over older conventional antipsychotics. Additional investigation is required to evaluate their efficacy and safety in children and adolescents.

- Elke HJ Krekels, John N van den Anker, Paola Baiardi, Massimo Cella, Katharine Y Cheng, Diana M Gibb, Hannah Green, Achille Iolascon, Evelyne M Jacqz-Aigrain, Catherijne AJ Knibbe, Gijs WE Santen, Ron HN van Schaik, Dick Tibboel, Oscar Della Pasqua. *Pharmacogenetics and paediatric drug development: issues and consequences to labelling and dosing recommendations*. Expert Opin Pharmacother. 2007 Aug;8(12):1787-99[9].

  This *TEDDY NoE* work argues that while pharmacogenetics (PGt) may be evolving rapidly, this does not in itself ensure that clinically relevant findings make their way into the label, particularly with paediatric indications.

[9] Full article available at: http://www.informapharmascience.com/doi/abs/10.1517/14656566.8.12.1787

All features that influence drug response must be considered when exploring the role of PGt factors on treatment effectiveness. While clinical research in children presents unique practical and technical challenges, many of these can be dealt with by using advanced study design and data analysis methods.

PGt enjoys privileged status in research protocols, with PGt factors commonly evaluated separately from other determinants of response, instead of alongside demographic or clinical covariates (for example: age, renal function). Even though this may be a new and incompletely understood area, the current lack of guidelines for incorporating PGt findings into label statements is no longer acceptable.

If PGt is to fulfill its potential contribution to drug development and ultimately to drug prescription, then academia, industry and regulatory agencies must pool resources for the revision of study design and data analysis requisites, bringing in model-based methodologies to enable accurate interpretation of results and to provide appropriate labelling recommendations.

- Ackers R, Murray ML, Besag FM, Wong IC. *Prioritizing children's medicines for research: a pharmacoepidemiological study of antiepileptic drugs*. Br J Clin Pharmacol. 2007 Jun;63(6):689-97[10].

  The *TEDDY NoE* project has investigated the prescribing epidemiology, in UK primary care, of newer antiepileptic drugs (AEDs) compared with conventional AEDs, with a view to identifying AEDs for further research. This activity meets the European Medicines Agency's recommendation for further research on newly marketed AEDs given the absence of information in available literature concerning use of AEDS in children in primary care.

  The study covered children aged 0–18 years who were prescribed an AED between 1993 and 2005, using the UK General Practice Research Database. Prescribing prevalence and incidence, stratified by age and AED, were calculated across the 7.721 subjects. The study found that 70% of the children were prescribed one drug and that overall prescribing prevalence for all AEDs had increased by 19%, with newer AED prescribing seeing a fivefold increase while conventional AED prevalence had declined by 17%. Lamotrigine made up 65% of the newer AED prescriptions and was the most prescribed newer drug for both the 2–11 years and 12–18 years age groups.

[10] Full article available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2000594

The researchers concluded that for children and adolescents in UK primary care there was a sharp increase in prescriptions of newer AEDs while conventional AEDs prescribing declined. Prevalence of vigabatrin fell since 1997, when safety warnings were issued in the UK concerning visual field defects. The researchers also noted that drugs showing rapid uptake - lamotrigine, topiramate, levetiracetam and indeed all newer AEDs - must be prioritized for further research because their safety has not been fully established.

- Sturkenboom M, Fatma E, Verhamme K, Herings R, Neubert A, Felisi M, Ceci A. *The TEDDY Network: Epidemiological Trends in Paediatric Drug Use in Europe*. EJHP Practice 2007; 13(6):22-24[11].

  Analysing data on what kinds of drugs are actually used in children will identify which ones must most urgently be studied for efficacy, for adequate formulations and for data on short and long term safety. The European Medicines Agency (EMEA) has drafted a list of more than 100 drugs that need research for paediatric use, but even within this list effective prioritisation is essential since it will not be possible to simultaneously conduct all the research implied.

  A specific *TEDDY NoE* objective is to set up a harmonised, integrated and reliable European database containing information on drug types and the extent of their use in children. Thus *TEDDY NoE* researchers are engaged in various activities related to assessing paediatric drug use, including the work reported in the European Journal of Hospital Pharmacy Practice (EJHP Practice - Vol.13 2007/Issue 6) which describes a survey of seventeen healthcare databases from ten European countries, covering some 9 million children up to 18 years old.

  The *TEDDY NoE* researchers conclude that the project is delivering important information about available data resources and about outpatient drug use in children. They also point out that there is insufficient data on in-hospital drug use and call for improved collaboration on this issue, targeting hospital pharmacists as key collaborators in a proposed pan-European network of data collection concerning in-hospital paediatric drug usage.

- Ceci A, Felisi M, Baiardi P, Bonifazi F, Catapano M, Giaquinto C, Nicolosi A, Sturkenboom M, Neubert A, Wong I. *Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years*. Eur J Clin Pharmacol 2006. Nov;62(11):947-52[12].

[11] Full article available at: http://www.eahp.eu/content/download/25594/167396/file/CoverStory22-24(1).pdf

[12] Full article available at:

http://www.springerlink.com/content/p003t463tw551331/?p=85fcbc5f12a34803a35d7b7e8ba7a98e&pi=8

This TEDDY evaluation of EMEA activities (1995 to 2005) in paediatric medicine looked at the number of drugs authorised for use in children as well as the paediatric studies supporting the Marketing Authorisation (MA).

The research team extracted data on EMEA-authorised drugs from European Public Assessment Reports (EPARs), thus identifying active substance, year of approval, the anatomical, therapeutic and chemical (ATC) code, indication, any orphan status, ages, and the type of clinical studies submitted.

The percentage of substances authorised for paediatrics was 33.3%. This percentage decreased or increased when different subsets of medicines were considered [medicines for children under 2 years (23.4%), N-ATC code drugs (6%) and orphan drugs (46.4%)]. A total of 165 trials were included in the MA dossiers of 51 drugs at the time of approval, and an additional 22 studies were added to the dossiers of 12 active substances submitted for paediatric variations. Pharmacokinetic (PK) and efficacy/safety studies were performed for 32 (52%) active substances, while either one PK or one efficacy/safety study was carried out for 43 (69%) and 45 (73%) substances respectively.

The report shows that while the total number of paediatric medicines approved by EMEA was stable over the 10-year period, an increasing in drugs to treat serious or orphan diseases has also been observed. In addition, under the Centralised Procedure run by EMEA to allow one marketing authorisation to be valid for all Europe, a valuable number of paediatric trials have been submitted to support drug approval.

- Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. *Has UK guidance affected general practitioner antibiotic prescribing for otitis media in children?* J Public Health (Oxf). 2008 Dec;30(4):479-86. Epub 2008 Sep 1.

  This study investigates the trends in diagnoses and antibiotic prescribing for otitis media in children in relation to guidance. Using the General Practice Research Database a time-trend analyses of diagnoses and antibiotic prescribing for otitis media in 3 months to 15 years old, between 1990 and 2006 was conducted. The study identifies that the reduction in antibiotic prescribing for otitis media predated guidance. The simultaneous decrease in prescribing for non-acute otitis media and increase for acute otitis media suggest diagnostic transfer, possibly to justify the decision to treat.

- Antonio F. Medina Claros, María José Mellado Peña, Fernando Baquero Artigao. *Bases para el uso clínico de fármacos en niños. Situación actual de uso de farmacos pediatricos en España.* An Pediatr Contin. 2008; 6(3):187-190.

The article is about the document "State of art of Drugs" (in press on Anales de Pediatria de Formación continuada). It has been written in collaboration with the Paediatric Spanish Society.

- ICK Wong, LYL Wong, ME Cranswick. *Minimising medication errors in children.* Arch Dis Child. 2009 Feb;94(2):161-4.

  This paper reviews the factors contributing to paediatric medication errors, including lack of appropriate paediatric formulations, communication issues between health professionals, dose calculation mistakes and inadequate clinical trial practice. This review also discuss risk reduction strategies such as electronic prescribing and computerised physician order entry (CPOE) systems which can significantly reduce paediatric medication errors in conjunction with pharmacist monitoring, improved communication and environments which promote best practice.

- S.McCarthy P. Asherson, D. Coghill, C. Hollis, M. Murray, L. Potts, K. Sayal, R. de Soysa, E. Taylor, T. Williams, ICK Wong. *Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults*. British Journal of Psychiatry in March 2009. Br J Psychiatry. 2009 Mar;194(3):273-7.

  This study analyses trends in prescribing prevalence and cessation of ADHD drug treatment among adolescents and young adults in the U.K.

- R. Ackers, FMC Besag, A Wade, ML Murray, ICK Wong. *Changing trends in antiepileptic drug prescribing in girls of child-bearing potential*. Arch Dis Child. 2009 Jun;94(6):443-7.

  This study characterises trends in prescribing carbamazepine (CBZ), sodium valproate (VPA) and lamotrigine (LTG) in adolescent females in the UK and examines possible reasons for changing trends. The analysis was cionducted using the UK General Practice Research Database between 1 January 1993 and 31 December 2006. The study shows that the practice of prescribing antiepileptic drugs in adolescents has changed gradually over the last decade.

- **BOOKS**

  - Della Pasqua O., Zimmerhackl L, Rose K. Study and Protocol Design for Paediatric Patients of Different Ages. Chapter of the book "Guide to Paediatric Clinical Research", edited by Klaus Rose and John van den Anker - Basel, Karger, 2007[13].

[13] Full article available at: http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowPDF&ArtikelNr=97781&Ausgabe=0&ProduktNr=232230&filename=97781.pdf

It explains the background of the US and EU paediatric legislation, gives an analysis of their impact, addresses key operational challenges in paediatric research, and develops a vision where this research needs to go.

In addition to describing the issues involved in the design of a clinical study for the paediatric population, it presents how PD/PK principles can be used to evaluate exposure – effect relationships in children. Furthermore, it addresses clinical considerations for bridging studies in children.

- External meetings: TEDDY participation in meetings organized by other institutions and organizations allows to diffuse the network results.
- Project Web site: TEEDY manages an own website (www.teddyoung.org).
- Other.

In addition of the above mentioned activities several personal informal talks have been held with health professionals, researchers, members of the national and European agencies (such as the EMEA) in order to establish relations that could foster future collaborations towards the best use of the Project results.

4. Receivers of the document

European Commission. To be diffused to the general public.

5. References to other documents

This document is an extract of the:

- TD-REP.016-Activity_Report_YearIV.doc;
- TD-REP.005-Plan_For_Using_Knowledge.doc.

Annex 1 – Publishable results of the *Plan for using knowledge*

N.A.